REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the claims. Claims 1, 6, 7, 8, 12, and withdrawn claim 17 have been amended to further clarify the claimed invention. Claims 9-11 have been cancelled without prejudice or disclaimer. Claims 26-71 are newly presented. After entry of the amendment, claims 1, 6-8, and 12-37 will be pending. Claims 13-25 have been withdrawn from consideration by the Examiner as drawn to a non-elected invention.

Applicants submit the amendments are supported throughout the specification, and particularly at pages 8-9 and 220-225. Specific support for the chimeric polypeptides of claims 27-31 can be found, for example, at page 24, beginning at line 20. Accordingly, the Amendments do not raise any issues of new matter.

Interview

On April 3, 2007, Applicants' representatives Denise Kettelberger and Eric DeMaster discussed the pending application with Examiner Huynh and Examiner Chan by telephone. The written description and enablement rejections were discussed. No agreement was reached.

Specification

The Office Action objected to the specification as containing informalities. The Brief Description of the Drawings contained several errors. The specification has been amended as suggested by the Examiner. Withdrawal of the objection is respectfully requested.

Enablement

Claims 1, 6-10, and 12 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicants respectfully traverse this rejection.

As an initial matter, claim 1 has been amended to recite an isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid sequence of residues 20 to 105 of SEQ ID NO:2. The claim encompasses 4 or fewer amino acid changes (*e.g.* amino acid substitutions, additions, or deletions) in the sequence defined by residues 20-105 of SEQ ID NO:2.

The full scope of claim 1 as amended is enabled by the specification. The specification describes techniques and guidelines for making EG-VEGF variants, including amino acid sequence comparison methods and exemplary and preferred amino acid substitutions (see specification at page 14, line 17 to page 16, line 15; page 30, line 22 to page 33, line 23; and Table 1 at page 32). Example 1 describes how to isolate cDNA clones encoding EG-VEGF, including the signal sequence finding algorithm used to identify cDNA clones. Example 2 describes how to use DNA comprising the coding sequence of mature EG-VEGF, for example, as a probe to screen for homologous DNA molecules encoding, for example, naturally occurring variants of EG-VEGF. Examples 3-6 describe how to express EG-VEGF in cells. Example 7 describes how to make antibodies that specifically bind EG-VEGF. Example 8 describes how to purify EG-VEGF using anti-EG-VEGF antibodies.

In view of the forgoing, Applicants submit the specification adequately teaches one of skill in the art to make the claimed polypeptides without undue experimentation using conventional methods. Even if the 4 or fewer amino acid changes in residues 20-105 of SEQ ID NO:2 resulted in a variant without ACE proliferation activity, the variant would still be useful as an antagonist or, as described in Example 7, as an immunogen for generating antibodies that bind EG-VEGF or identifying antibodies that bind EG-VEGF. One of skill in the art would be able to make and use the variants encompassed by claim 1 as amended without undue experimentation.

For example, the specification discloses that variants of native EG-VEGF can be antagonists of a biologic activity of native EG-VEGF (see, for example, page 24, lines 12-14 and 17-18) and describes techniques and guidelines for making EG-VEGF variants, including amino acid sequence comparison methods, exemplary and preferred amino acid substitutions, and guidelines for selecting substitutions that result in substantial changes in the biological activity of EG-VEGF (see, for example, page 14, line 17 to page 16, line 15 and page 30, line 22 to page 33, line 23). Bullock et al. confirms Applicants teaching that variants of EG-VEGF are useful as antagonists of native EG-VEGF. Bullock disclosed the N-terminus substituted EG-VEGF bound EG-VEGF receptors prokineticin 1 (PKR1) and prokineticin 2 (PKR2) and antagonized binding of unsubstituted EG-VEGF to PKR1 or PKR2 as well as EG-VEGF-induced cell proliferation activity (see pages 585-586, Table 3, and Figs. 2A, 5A, and 5B).

The Office Action raises three issues with respect to enablement. First, the Office Action alleges the specification does not enable an isolated EG-VEGF polypeptide having at least 95%

amino acid sequence identity with the amino acid sequence of residues 20 to 105 of SEQ ID NO:2 that promotes proliferation of ACE cells. Second, the Office Action alleges the specification does not enable an isolated polypeptide comprising an amino acid sequence of SEQ ID NO:2 or amino acid residues 20-105 of SEQ ID NO:2 and induces proliferation of ACE cells. Third, the Office Action alleges the specification does not enable any native sequence or allelic variant of an EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid sequence of residues 20 to 105 of SEQ ID NO:2. The rejections respectfully traversed. Each is addressed in the order presented above.

1. The specification fully enables EG-VEGF polypeptides having at least 95% amino acid sequence identity with the amino acid sequence of residues 20 to 105 of SEQ ID NO:2 (mature form of EG-VEGF).

The Office Action alleges the specification has not identified which amino acids within the one or more internal domains of the full-length sequence SEQ ID NO:2 or the mature sequence (amino acid residues 20-105 of SEQ ID NO:2) can be substituted, deleted, and/or added such that the resulting modified EG-VEGF polypeptide functions to promote proliferation of ACE cells. Without such guidance, the Office Action alleges the changes which can be made to the full-length EG-VEGF polypeptide sequence or mature EG-VEGF polypeptide sequence and maintain the endothelial cell proliferative activity is unpredictable. Applicants respectfully do not agree.

To be enabling, a disclosure need only provide a reasonable correlation to the scope of the claims. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied (*In re Fischer*, 427 F.2d 833, 839 (CCPA 1970)). For a claimed genus, representative examples coupled with a statement applicable to the genus as a whole are ordinary sufficient to comply with the enablement requirement (MPEP § 2164.02).

Contrary to the Examiner's position in the Office Action, the disclosure of a test containing a recitation of every species in the claim's scope is not necessary for establishing enablement under 35 U.S.C. § 112, first paragraph. *In re* Wands, 858 F.2d 731 (Fed. Cir. 1998). A substantial amount of experimentation is permissible if the experimentation is routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the

experimentation should proceed. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (emphasis added); see also *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976).

Applying these standards, Applicants submit the specification contains sufficient disclosure to enable the scope of the claimed genus of EG-VEGF polypeptides. The specification describes techniques and guidelines for making EG-VEGF variants, including amino acid sequence comparison methods and exemplary and preferred amino acid substitutions (see specification, for example, at page 14, line 17 to page 16, line 15; page 30, line 22 to page 33, line 23; and Table 1 at page 32). Example 1 describes how to isolate cDNA clones encoding EG-VEGF, including the signal sequence finding algorithm used to identify cDNA clones. Example 2 describes how to use DNA comprising the coding sequence of mature EG-VEGF, for example, as a probe to screen for homologous DNA molecules encoding, for example, naturally occurring variants of EG-VEGF. Examples 3-6 describe how to express EG-VEGF in cells. Example 7 describes how to make antibodies that specifically bind EG-VEGF. Example 8 describes how to purify EG-VEGF using anti-EG-VEGF antibodies. Example 14 describes how to screen EG-VEGF polypeptides for ACE cell proliferation activity.

In view of the guidance provided in the specification as discussed above, Applicants submit any amount of experimentation required to enable the full scope of the claims is routine. At the very least, the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

The level of skill in the art of biotechnology is high and advanced. At the very least, one of skill in the art would have been able to identify the claimed EG-VEGF variants using the EST techniques, hybridization probes, and/or anti-EG-VEGF antibodies described in the specification without undue experimentation. The EST, hybridization, and antibody assays described in the specification are well known in the art and the Office Action has not shown that undue experimentation would be required to use these methods. Applicants' post filing publication, in which mouse EG-VEGF was identified using an EST highly related to human EG-VEGF, confirms the teachings of the specification. See LeCouter et al., 2003, *Endocrinology*, 144:2606-2616. Mouse EG-VEGF has 88% identity to amino acid residues 20-105 of SEQ ID NO:2 and induces proliferation of ACE cells (see Figures 1B and 7A in LeCouter et al.).

Citing Attwood et al. and Skolnick et al., the Office Action alleges the relationship between an amino acid sequence and its activity is unpredictable and that current sequence based

methods for predicting structure and function are inadequate and unreliable. Citing Mikayama et al., the Office Action alleges a single amino acid change can have dramatic effects on a protein's function.

In contrast to the Examiner's assertions, Applicants cited Brenner et al., 1998, *Science*, 95:6073-6078. Brenner discloses that % sequence identity comparison methods are adequate and useful for predicting shared function. Brenner studied domains of proteins in the Protein Data Bank creating a database of domains used to assess sequence comparison methods. Using this database, Brenner found pairwise sequence comparison methods were capable of detecting almost all relationships between proteins whose sequence identities were greater than 30% (Brenner at Abstract at page 6073 and figure 3 at page 6075). Pairwise sequence comparison methods that utilized statistical scores, such as E-values, recognized greater than 90% of the homologous pairs with 30-40% identity (Brenner at page 6077) leading Brenner to conclude that E-values give fairly accurate estimates of the significance of pairwise sequence matches and that the homologous proteins found by sequence comparison can be distinguished with high reliability from the huge number of unrelated pairs. (Brenner at pages 6077-6078). The Brenner study validated the use of sequence comparison methods to establish that % sequence identity comparisons greater than 30% are predictive of shared function.

The Office Action dismisses the teachings of Brenner et al. by merely asserting that Brenner et al. does not teach sequence identity comparison for the claimed EG-VEGF polypeptides or the function of EG-VEGF. The same rational can be applied to dismiss the teachings of Attwood et al., Skolnick et al., and Mikayama et al. None of these references teaches sequence identity comparison for the claimed EG-VEGF polypeptides or the function of EG-VEGF.

Contrary to the alleged teachings of Mikayama et al. Bowie et al. discloses that proteins are surprisingly tolerant of amino acid substitutions (Bowie et al., 1990, *Science*, 247:1306-1310 (copy enclosed in response file on)). The post filing publications of LeCouter et al., 2003, *Endocrinology*, 144:2606-2616; Masuda et al., 2002, *Biochem. Biophys. Res. Commun.*, 293:396-402; and Kisliouk et al., 2005, *Endocrinology*, 146:3950-3958 confirm the teachings of Bowie et al. with respect to EG-VEGF. Mouse EG-VEGF has 88% identity to amino acid residues 20-105 of SEQ ID NO:2 and induces proliferation of ACE cells (see Figures 1B and 7A in LeCouter et al.). Masuda et al. identified rat EG-VEGF, which has approximately 91%

identity with amino acid residues 20-105 of SEQ ID NO:2 and induces mitogenesis of ACE cells Kisliouk et al. identified bovine EG-VEGF, which has approximately 88% identity with amino acid residues 20-105 of SEQ ID NO:2 and induces proliferation of endocrine gland-derived endothelial cells. See the amino acid sequence alignment of identified EG-VEGF species in Table 1.

Table 1

```
CLUSTAL W (1.8) multiple sequence alignment of EG-VEGF species

 HuEG-VEGF       AVITGACERDVQCGAGTCCAISLWLRGLRMCTPLGREGEECHPGSHKVPFFRKRKHHTCP
 RtEG-VEGF       AVITGACERDVQCGAGTCCAISLWLRGLRLCTPLGREGEECHPGSHKIPFFRKRQHHTCP
 BvEG-VEGF       AVITGACERDVQCRAGTCCAVSLWLRGLRVCTPLGRAGEECHPGSHKVPFFRKRQHHACP
 MsEG-VEGF       AVITGACERDIQCGAGTCCAISLWLRGLRLCTPLGREGEECHPGSHKIPFLRKRQHHTCP
                 **********:** ******:********:****** **********:**:***:**:**

 HuEG-VEGF       CLPNLLCSRFPDGRYRCSMDLKNINF
 RtEG-VEGF       CSPSLLCSRFPDGRYRCSQDLKNVNF
 BvEG-VEGF       CLPNLLCSRGLDGRYRCSTNLKNINF
 MuEG-VEGF       CSPSLLCSRFPDGRYRCFRDLKNANF
                 * *.*****  ******  :*** **
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	Species	% Identity to Mature Human EG-VEGF*	Reference
HuEG-VEGF	human	100	Specification at Figure 16A
RtEG-VEGF	rat	91	Masuda et al., 2002, *Biochem. Biopyhs. Res. Commun.*, 293:396-402.
BvEG-VEGF	bovine	88	Kisliouk et al., 2005, *Endocrinology*, 146:3950-3958.
MuEG-VEGF	mouse	88	LeCouter et al., 2003, *Endocrinology*, 144:2606-2616.

* Amino acid residues 20-105 of SEQ ID NO:2.

Citing Bullock et al. and Negri et al., the Office Action alleges that adding, deleting, or substituting even one amino acid at the N-terminus of EG-VEGF results in an EG-VEGF variant that is completely devoid of biological activities. Applicants respectfully do not agree.

Applicants submit the effect of the N-terminus amino acid substitutions and deletions disclosed in Bullock et al. with respect to the endothelial cell proliferation activity EG-VEGF (or any changes in the angiogenic activity of EG-VEGF that may be implied from Negri et al., which

discloses Bv8 variants having N-terminus amino acid substitutions similar to those disclosed in Bullock et al.) are not surprising in view of Applicants' teachings. The specification shows exemplary conservative substitutions (Table 1) and discloses that substantial changes in biological activity are made by selecting substitutions that are less conservative than those in Table 1. See the specification, for example, at pages 31-32. The specification also discloses selecting substitutions that differ significantly on their effect in maintaining the structure of the polypeptide backbone in the area of the substitution, charge or hydrophobicity, or the bulk of the side chain.

Figure 2, panel A in Bullock et al. discloses that substituting amino acid residue 20 with M (A1M) significantly reduces the endothelial cell proliferative activity of the substituted EG-VEGF . Applicants note that at concentrations above $1X10^{-9}$ M, A1M substituted EG-VEGF is not "completely devoid of biological activities" as asserted on page 12 of the Office Action but retains the ability to induce proliferation of the endothelial cells albeit at a significantly reduced level as compared to the unsubstituted EG-VEGF. Table 1 indicates that changes in EG-VEGF function can be made by substituting A with an amino acid other than V, L, or I. In view of Applicants' disclosure, it would not be surprising that substituting A with M would produce an EG-VEGF variant having reduced cell proliferation activity.

The Office Action disagrees with Applicants' assertion that EG-VEGF and VEGF were known to exist in families having high amino acid sequence identity. Citing Carmeliet et al. and Bullock et al., the Office Action alleges EG-VEGF and VEGF are structurally similar and work though different receptors. Applicants' submit the Office Action has misconstrued Applicants comments provided in the previous response. VEGF was cited as an example for the proposition that angiogenic factors in general were known to exist in families having high amino acid sequence identity (*e.g.*, variants and homologs). The specification demonstrates that EG-VEGF is an angiogenic factor. Therefore, one of skill in the art would have reasonably expected EG-VEGF, like other angiogenic factors, to be a member of a protein family (including variants and homologs) having high amino acid sequence identity.

In view of the forgoing, Applicants submit an isolated EG-VEGF polypeptide having at least 95% amino acid sequence identity with the amino acid sequence of residues 20 to 105 of SEQ ID NO:2 wherein the polypeptide promotes proliferation of ACE cells could have been

made without undue experimentation in view of the guidance provided in the specification. Withdrawal of the enablement rejection is respectfully requested.

2. The specification fully enables an isolated polypeptide comprising SEQ ID NO:2 (full-length EG-VEGF) or amino acid residues 20-105 of SEQ ID NO:2 (mature EG-VEGF).

The Office Action alleges claims 6 and 8 lack enablement as the term "comprising" expands the polypeptide sequence of amino acids 20-105 to include additional amino acids at the N- terminal and/or C-terminal of the polypeptide.

Claims 1, 6, 7, and 8 have been amended to further clarify the claimed invention. The specification discloses that EG-VEGF, for example, can have a signal sequence. Full-length EG-VEGF (SEQ ID NO:2) includes a signal sequence of about 19 amino acids (see Figure 16A). The specification discloses selecting mammalian or prokaryotic signal sequences (dependent on the host cell) having a specific cleavage site at the N-terminus of mature EG-VEGF that can be used to direct secretion of EG-VEGF (page 41, lines 3-16). The specification also discloses chimeric molecules comprising EG-VEGF and a heterologous peptide. For example, EG-VEGF can be fused with an epitope tag, such as a poly-his tag, to facilitate detection or purification or fused with an immunoglobulin to form a bivalent chimeric molecule (page 35, line 13 to page 36, line 11, and Example 4). Methods for making chimeric molecules comprising the EG-VEGF polypeptides are well known. The claims have been amended to clarify this point. Applicants therefore submit claims 1, 6, 7, and 8 and new claims 30-37 are sufficiently enabled.

3. The Office Action alleges claims 9, 10, and 11 lack enablement as the specification does not provide any guidance regarding alternative spliced, naturally occurring, or allelic variant forms of EG-VEGF. Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claims 9, 10, and 11 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the cancelled subject matter in a continuation application.

Applicants note that the subject matter of claims 9-11 falls within the scope of claims to a polypeptide having at least 95 percent identity to residues 20-105 of SEQ ID NO:2 (claim 1). Polypeptides of claim 1 may include allelic variants, alternative spliced, or naturally occurring forms of EG-VEGF that meet the recited limitations.

For the reasons discussed above, Applicants submit the specification fully enables the claims. Applicants assert the guidance and examples provided in the specification are sufficient to enable one of skill in the art to make and use the claimed EG-VEGF polypeptides without undue experimentation. Withdrawal of the rejection is respectfully requested.

Written Description

Claims 1, 6-10, and 12 were rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. Applicants respectfully traverse this rejection.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. MPEP § 2163(I) (emphasis added). As noted in the Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, ¶1, "Written Description" Requirement ("the guidelines"), there is a "strong presumption" that an adequate written description of the claimed invention is present when the application is filed, 66(4) Fed Reg. 1099, 1105 (2001); see also, *In re Wertheim,* 191 USPQ 90,97 (CCPA 1976).

An Applicant may show possession of an invention by disclosure of sufficiently detailed, relevant identifying characteristics (i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between structure and function, or some combination of such characteristics) that provide evidence that Applicant was in possession of the claimed invention. *Enzo Biochem v. Gen-Probe*, 323 F.3d 956, 964 (Fed. Cir. 2002); MPEP § 2163(II)(3)(A)(a). An actual reduction to practice, however, is not required for written description. *Falkner v. Inglis*, No. 05-1324, slip. op. at 13 (Fed. Cir. May 26, 2006).

The written description requirement must be applied in the context of the particular invention and state of the knowledge. *Capon v. Eschar*, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). It is unnecessary to spell out every detail of the invention in the specification. Only enough must be included to convince a person of skill in the art that the inventor possessed the invention. *Falkner v. Inglis*, No. 05-1234, slip. op. at 14 (Fed Cir. May 26, 2006) (citing *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.,* 424 F.3d 1336, 1345 Fed. Cir. 2005).

Applying these standards, Applicants submit the specification sufficiently describes the claimed genus of polypeptides. Claim 1 has been amended to recite an isolated EG-VEGF

polypeptide having at least 95% amino acid sequence identity with the amino acid sequence of residues 20 to 105 of SEQ ID NO:2. The claim encompasses 4 or fewer amino acid substitutions, mutations, and/or deletions in the sequence defined by residues 20-105 of SEQ ID NO:2.

As discussed above, the specification describes techniques and guidelines for making EG-VEGF variants, including amino acid sequence comparison methods and exemplary and preferred amino acid substitutions (see specification at page 14, line 17 to page 16, line 15; page 30, line 22 to page 33, line 23; and Table 1 at page 32). Example 1 describes how to isolate cDNA clones encoding EG-VEGF, including the signal sequence finding algorithm used to identify cDNA clones. Example 2 describes how to use DNA comprising the coding sequence of mature EG-VEGF, for example, as a probe to screen for homologous DNA molecules encoding, for example, naturally occurring variants of EG-VEGF. Examples 3-6 describe how to express EG-VEGF in cells. Example 7 describes how to make antibodies that specifically bind EG-VEGF. Example 8 describes how to purify EG-VEGF using anti-EG-VEGF antibodies.

The level of skill in the art is high and advanced. In view of the description provided in the specification and the high level of skill in the art, Applicants submit one of skill in the art would have recognized the spectrum of EG-VEGF polypeptides encompassed by the claims.

The Office Action alleges the specification has not identified which amino acids within the one or more internal domains of the full-length sequence SEQ ID NO:2 or the mature sequence (amino acid residues 20-105 of SEQ ID NO:2) can be substituted, deleted, and/or added such that the resulting modified EG-VEGF polypeptide functions to promote proliferation of ACE cells. Without such disclosure, the Office Action alleges one of skill in the art would not be able to reasonably conclude that the inventor had possession of the claimed invention. Applicants respectfully do not agree.

Applicants direct the Examiner's attention to Example 14 of the USPTO Revised Written Description Guidelines Training Materials. Example 14 outlines a written description analysis of a polypeptide claim that satisfies the requirement under 35 U.S.C. § 112, first paragraph. The claim in Example 14 is directed to a genus of polypeptides having at least 95% identity to a reference sequence (SEQ ID NO:3) and a specific activity. The specification provided a novel and unobvious polypeptide sequence (SEQ ID NO:3) having a specific activity and an assay for identifying other proteins having the claimed specific activity. The specification did not disclose

any variants of the polypeptide sequence. Example 14 in the written description guidelines states:

> The procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art. . .
>
> The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by members of the genus.

Applying the analysis set forth in Example 14 of the written description guidelines, Applicants submit the specification sufficiently describes the claimed genus of EG-VEGF polypeptides. Similar to the claim analyzed in Example 14, Applicants' claims are directed to a genus of EG-VEGF polypeptides that have 95% identity to mature EG-VEGF and promote proliferation of ACE cells. Example 1 describes how to isolate cDNA clones encoding EG-VEGF, including the signal sequence finding computer algorithm used to identify the cDNA clones. Examples 2-6 teach expression of EG-VEGF. Example 14 describes an assay for detecting the cell proliferation activity of EG-VEGF, which can be used to identify variants have the claimed cell proliferation activity. Specific nucleic acid sequences encoding EG-VEGF (nucleotides 91-405 of SEQ ID NO:1 and SEQ ID NO:3) and amino acid sequence (SEQ ID NO:2) of EG-VEGF are taught in the specification. Methods for making EG-VEGF variants, including preferred amino acid substitutions are also disclosed. See, for example, page 31, line 24 to page 33, line 23.

The Office Action dismisses Applicants arguments based on Example 14 of the Written Description Guidelines by merely asserting the addition of functional language without identifying which amino acids are critical for the function of the protein is not sufficient to satisfy the written description requirement. The Office Action fails to provide a legal basis in case law or the MPEP for the assertion that Applicants must describe which amino acids are critical for the function of the protein to satisfy the written description requirement. Moreover,

the Office Action fails to provide any reasoning why the analysis described in Example 14 of the Written Description Guidelines no longer satisfies the written description requirement.

Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claims 9, 10, and 11 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the cancelled subject matter in a continuation application. Applicants note that the subject matter of claims 9-11 falls within the scope of the claims as long as the polypeptide has at least 95 percent identity to residues 20-105 of SEQ ID NO:2. The polypeptides of the claims may include allelic variant, alternative spliced, or naturally occurring forms of EG-VEGF that meet the recited limitations.

For at least these reasons, Applicants respectfully submit the specification fully describes the claimed invention. Removal of the written description rejection is respectfully requested.

New Matter

Claim 10 was rejected under 35 U.S.C. § 112, second paragraph, as lacking written description. This is a new matter rejection. Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claim 10 has been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the cancelled subject matter in a continuation application.

Applicants note that allelic variants having at least 95 percent identity to residues 20-105 of SEQ ID NO:2 fall within the scope of pending claim 1 and thus are not abandoned subject matter.. The polypeptides of the remaining claims (claims 1, 6-8, 26-37 and withdrawn claims 13-25) include allelic variant forms of EG-VEGF that meet the recited elements of the claims.

Priority

The Office Action acknowledges that claims 6, 7, 8, 11, and 12 have an effective filing date of at least September 7, 2000, the filing date of provisional application No. 60/230,978 (hereinafter the '978 application). With respect to claims 1, 9, and 10, the Office Action alleges the claims are only entitled to the filing date of the instant application, which is October 22, 2003. Applicants do not agree and submit all pending claims are entitled to a priority date of at least July 26, 1999, the filing date of provisional application 60/145,698 (hereinafter the '698 application).

As detailed in prior responses, human EG-VEGF (SEQ ID NO:2) is referred to as PRO1186 (SEQ ID NO:165; Figure 66) in the '698 application. The '698 application discloses that the term "PRO1186" or "PRO1186 polypeptide" encompasses native-sequence PRO1186 polypeptide variants. See, for example, page 44, line 29 to page 45, line 20. The native-sequence PRO1186 polypeptide can be a mature or full-length native sequence PRO1186 comprising the amino acid sequence of Figure 66 (SEQ ID NO:165). See, for example, page 46, line 19 to page 47, line 7.

Fragments of the native polypeptide include, but are not limited to, polypeptide variants from which the native N-terminal signal sequence has been fully or partially deleted. See, for example, page 47, lines 8-10. Analysis of the full-length PRO1186 sequence indicated that amino acids 1-19 of PRO1186 (SEQ ID NO:165) comprise a signal sequence. See, for example, page 279, lines 4-5. In addition, the '698 application defines a "PRO1186 polypeptide variant" as an active PRO1186 polypeptide having at least about 95% amino acid sequence identity with residues 20 to 105 of the PRO1186 polypeptide shown in Figure 66 (SEQ ID NO:165). See, for example, page 55, lines 21-24 and page 77, lines 14-29. The specification describes techniques and guidelines for making PRO1186 variants, including amino acid sequence comparison methods and exemplary and preferred amino acid substitutions. See, for example, pages 134-137. The Example 38 in the '698 application describes an assay for determining if a molecule has cell proliferation activity and demonstrates that PRO1186 induces proliferation of ACE cells (see, for example, pages 280-281).

The above referenced pages and figures from the '698 application are attached for the Examiner's convenience.

The Office Action asserts none of the PCT and U.S. provisional application enable or adequately describe EG-VEGF polypeptides having at least 95% amino acid sequence identity with amino acid residues 20-105 of SEQ ID NO:2. Applicants strongly do not agree.

The '698 application satisfies the enablement and written description requirements for the same reasons provided herein for the instant application. For example, the '698 application describes techniques and guidelines for making PRO1186 variants, including amino acid sequence comparison methods and exemplary and preferred amino acid substitutions, and describes how to screen PRO1186 variants for ACE cell proliferation activity.

In view of the evidence and reasoning provided herein, Applicants submit the '698 application fully enables and adequately describes the claims as required by 35 U.S.C. § 112, first paragraph. Applicants claims are therefore entitled to a priority date of at least July 26, 1999, the filing date of the '698 application.

Anticipation

Claims 1, 9, and 10 were rejected under 35 U.S.C. § 102(a) and claims 1 and 6-12 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. 6,485,938 (hereinafter the '938 patent). Applicants respectfully traverse this rejection.

The Office Action alleges the '938 patent is entitled to a priority date of November 16, 1999. For the reasons discussed above, Applicants' claims are entitled to at least a priority date of July 26, 1999, the filing date of the '698 application. The filing date of the '698 application, July 26, 1999, predates the earliest priority date of the '938 patent. Therefore, the '938 patent is not prior art under §§ 102(a) or 102(e). Withdrawal of the rejection is respectfully requested.

Claims 1 and 6-12 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. 7,119,177, filed on November 15, 2001 (hereinafter the '177 patent). Applicants respectfully traverse this rejection.

The basis of this rejection is that the '177 patent claims priority to provisional application No. 60/141,037, filed on June 23, 1999 (hereinafter the '037 application). The '037 application, however, does not disclose SEQ ID NO:2 (EG-VEGF) of the present application or SEQ ID NO:371 (PRO1186) of the '177 patent. As discussed above, Applicants' claims are entitled to at least a priority date of July 26, 1999, the filing date of the '698 application. The filing date of the '698 application, July 26, 1999, therefore predates the filing date (November 15, 2001) of the '177 patent.

With respect to PRO1186, Applicants note the '177 patent also claims priority to the '698 application. The present application and the '177 therefore have the same priority date and are not prior art to one another under § 102(e). Withdrawal of the election is respectfully requested.

Nonstatutory Double Patenting

Claims 1 and 6-13 were rejected on the grounds of non-statutory double patenting as being unpatentable over claims 1-4 of U.S. 7,119,177. Applicants acknowledge the rejection

and respectfully request that the rejection be held in abeyance until allowable subject matter is indicated.

Conclusion

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: July 5, 2007

Eric E. DeMaster
Reg. No. 55,107
EED:jrm

23552
PATENT TRADEMARK OFFICE